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KANSAS CITY, MO 64112			DATE MAILED: 12/11/2006	

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/707,980	Applicant(s) BENTWICH, ITZHAK	
	Examiner Jon Eric Angell	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 September 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 69-88 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 69-88 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 29 January 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>10/6/06</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Action is in response to the communication filed on 9/25/2006.

The amendment filed 9/25/2006 is acknowledged and has been entered.

Claims 69-88 are currently pending in the application and are addressed herein.

Election/Restrictions

It is noted that the Election/Restriction requirement mailed 3/16/2006 was applicable to the claims pending at that time, specifically, claims 65-68. However, claims 65-68 have been cancelled and claims 69-88 are now pending in the application. In the pending claims, claim 69 is the only independent claim. Accordingly all pending claims encompass an isolated nucleic acid that is between 19 and 140 nucleotides in length and which comprises a sequence of SEQ ID NO: 142700, as indicated in claim 69. Therefore a search using SEQ ID NO:142700 would be sufficient for searching the instant claims, and there would not be a serious search burden to perform this search. Accordingly, the Restriction/Election requirement is moot as it pertains to the currently pending claims. Therefore, the Restriction/Election requirement is withdrawn and all pending claims are examined herein.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 10/6/2006 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 69-86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 69, line 5, and claim 72, line 5, the phrase "at least 92/131" is vague and unclear. Appropriate clarification is required.

Claim 72 does not further limit claim 69 because claim 69 already encompasses nucleic acids that consist of at least 19 consecutive nucleotides of SEQ ID NO: 142700.

In claims 79 and 80, the phrase "at least 14/22 complementary" is vague and unclear. Appropriate clarification is required.

In claims 85 and 86 the phrase, "a gene expression inhibition system" is vague and unclear. Appropriate clarification is required.

Claims 70, 71, 73-78, 81-84 are included in the rejection because they are dependent claims which encompass all of the embodiments of the dependent claims, including the indefinite embodiments.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claims 69-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

MPEP §2163.06 notes:

If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

MPEP §2163.06 further notes:

When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure.

No support has been found in the specification as originally filed for the phrases " at least 92/131" recited in claims 69 and 72, and " at least 14/22 complementary" recited in claims 79 and 80, nor has support been found for the size limitation of 19-140 nucleotides (e.g. as recited in claim 69). Also, support cannot be found for "an RNA equivalent of (a)" as indicated in claims

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69 and 72. It is acknowledged that Applicants have indicated in the communication filed 9/18/2006 that support for the new claims can be found throughout the specification, including at paragraphs 38-41, 45-47, 174 and 175, as well as in Table 10 (lines 267-330), Table 4 (lines 1215-1222 and 1628-1632), and Table 7 (lines 188035-188829), and also in originally filed claims 1-3. It is noted that the specification, including paragraphs 38-41, 45-47, 174 and 175 and originally filed claims 1-3 were reviewed and support for the indicated limitations could not be found. Furthermore, the instant specification, which is over 8400 pages in length, was thoroughly searched but Tables 4, 7 and 10 could not be located. Applicants are asked to review the specification available in public PAIR and to identify the pages and line numbers of public pair where Tables 4, 7, and 10 can be found (as well as the lines of these Tables to which applicants refer).

Since support for the new limitations indicated above could not be found, a rejection of the indicated claims, as well as all claims depending therefrom, are properly rejected under 35 U.S.C. § 112, first paragraph.

Claims 69-86 are also rejected under 35 U.S.C. 112, first paragraph because the claims appear to encompass sequences which are different from the disclosed sequences, but which have not been adequately described in the specification.

For instance, claims 69 and 72 appear to encompass sequences that are "at least 92/131 identical to (a) or (b)", which is interpreted as having at least 70% identity to SEQ ID NO: 142700 (or an RNA equivalent). Therefore, the claims encompass an extremely large genus of molecules which are variants of SEQ ID NO: 142700 (or an RNA equivalent). This large genus

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appears to be represented in the specification by only SEQ ID NOs: 142700, 140670, 140732, 2 and 9. Thus, applicant has express possession of only 5 specific sequences of a genus which comprises an enormous number of different possibilities.

The written description guidelines note regarding such genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, no common element or attributes of the sequences are disclosed. No structural limitations or requirements which provide guidance on the identification of sequences which meet the functional limitations is provided.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that:

"In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See *Fiers*, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing *Amgen*). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

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It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that: "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

"...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acid sequences encompassed by the claims, other than those expressly disclosed, which represent variant nucleic acid sequences which have the desired function. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

In the instant application, only the specifically identified SEQ ID NOs are described.

Claim Rejections - 35 USC §§ 101 and 112

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 69-86 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or, alternatively, a well established utility.

In their broadest embodiments, the claims are drawn to probes, vectors and gene expression systems comprising polynucleotides between 19-140 nucleotides in length sharing at least "19/131" (70%?) identity with SEQ ID No. 142700 or an RNA equivalent.

A review of the specification, which is over 8,4000 pages long, finds general assertions and statements that the present invention relates to a group of bioinformatically detectable novel genes, which Applicant refers to as "genomic address messenger" or "GAM" genes, which are believed to be related to the micro RNA (miRNA) group of genes.

The specification teaches that Micro RNAs (miRNAs), are short ~22nt non-coding regulatory RNA oligonucleotides, found in a wide range of species, believed to function as specific gene translation repressors, sometimes involved in cell-differentiation.

The specification makes general statements that the bioinformatically detectable sequences, GAMs, and the miRNAs they may encode may have utility for regulating target genes and possibly for treating disease.

However, the specification provides no direct or indirect evidence for any specific, substantial, or credible utility of the instantly claimed RNAs encoded by SEQ ID NO:142700 (or an RNA equivalent). There is no disclosure indicating or suggesting that SEQ ID NO:142700 has itself ever been isolated or examined in any way, nor any evidence that the claimed RNA has, in fact, been isolated or prepared or studied or examined under any conditions. Any asserted utility for the claimed sequences appears to be merely speculation based on "bioinformatics,"

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homology, and secondary structure predictions suggesting that the encoded RNAs are miRNAs because they have a miRNA-like hairpin structure and some degree of sequence homology to some unidentified target sequence. On this basis, and since other miRNAs are known to have gene expression modulating properties, Applicant appears to be asserting that the bioinformatically detectable sequences, or GAMs, such as the RNAs encoded by SEQ ID NO:142700 also have utility.

However, that utility has not been clearly defined, nor does the prior art search of SEQ ID NO:142700 provide any substantial evidence to show that the RNAs of the size now claimed have any substantial, specific, or credible utility.

Applicant has not shown, and there is no evidence in the prior art to suggest, that the RNAs now claimed are expressed in any cell whatsoever. While there may be some purported links or sequence homology connections between the instantly claimed sequences and RNAs to known gene, which may have a utility, Applicant has not pointed or directed the Examiner to those portions of the 8,400 plus pages of specification, drawings, and sequence disclosures that might substantiate a utility.

Indeed, the asserted utility and target gene of this and thousands of other miRNA-like sequences appears to be based purely on bioinformatic methods for predicting RNA folding and potential gene targets.

Krutzfeldt et al. (2006) *Nature Genetics* 38:514-519 state that, in general, the basis for these types of prediction programs is the degree of sequence complementarity between a miRNA and a target UTR, including the presence of a consecutive string of base pairs at the 5' end of the miRNA known as a 'seed' or 'nucleus', and the cross-species conservation of this binding site.

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On average, 200 genes are predicted to be regulated by a single miRNA. The authors further state that reviewing the data provided by these algorithms determining candidate targets uncovers the entire gamut of gene categories, such as transcription factors, protein kinases, vesicular trafficking molecules and membrane receptors, suggesting that there is no apparent bias towards one particular function.

Accordingly, while the ability to predict hairpin-like structures and potential gene targets from genomic sequence information appears to be within the state of the art, Krutzfeldt et al. teach that validating the true biological function of any predicted miRNA sequence requires analyzing miRNA expression patterns, as well as testing the effects of miRNA overexpression and underexpression under different conditions in living cells *in vitro* and *in vivo*.

Thus, while these methods, too, are within the level of skill in the art, Applicant has presented no evidence that any of these validation techniques have, in fact, been carried out with regard to the instantly claimed sequences. That is, no evidence can be found verifying or even suggesting that the sequences encompassed by the claims, including SEQ ID NO:142700, RNA equivalents, etc., actually gives rise to miRNAs in any cell or organism, and if it does, Applicant has not described or shown any specific, substantial, or credible utility for the expressed miRNA. The fact that an miRNA can regulate gene expression is not specific or substantial because 1) this activity is inherent to almost any miRNA, and 2) because Applicant has not taught any use or purpose for the inhibitory activity nor proposed any specific utility for the asserted down regulation of the target gene of the RNA now claimed.

For instance, Applicant has not provided evidence that the nucleic acid sequences encompassed by the claims play any role in the predisposition of humans or other mammals to

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disease. There is no evidence to suggest that the nucleic acid sequences purportedly are up or down regulated in response to foreign agents or disease states or that the expression or targeting of miRNAs of the instant invention would provide any real world information for a specific use other than general knowledge as to understanding the biological function of the miRNA.

The specification generally asserts that a utility of the novel oligonucleotides of the present invention is detection of GAM oligonucleotides and of GR (Genomic Record) polynucleotides—that diagnosis of expression of oligonucleotides of the present invention may be useful for research purposes, in order to further understand the connection between the novel oligonucleotides of the present invention and disease and disease diagnosis and prevention purposes, and for monitoring disease progress.

However, none of these asserted uses meet the three-pronged requirement of 35 U.S.C. § 101 regarding utility, namely, that the asserted utility be credible, specific and substantial.

This asserted utility is neither specific nor substantial. Since the same can be done with any polynucleotide, the asserted utility is not specific. Also, because the specification does not disclose any specific function for SEQ ID NO:142700, aside from indicating that it may encode an miRNA, it is unclear how or why one of skill in the art would use the information obtained by measuring SEQ ID NO:142700 or its DNA complements or expressed RNAs for any particular purpose aside from general research. Further, since Applicant does not identify whether abnormal SEQ ID NO:142700 expression is causally related to any disease or condition, or whether abnormal SEQ ID NO:142700 function (e.g., a polymorphism) predisposes anyone to any disease or condition, the only recognizable utility of diagnostic probes is as tools for scientific research, and with no indication that anything useful will be discovered. Therefore, the

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asserted utility is not substantial since the application provides no teaching regarding how to use the sequences or expression data for any practical purpose beyond the art-recognized methods of gene expression analysis.

Accordingly, polynucleotide probes derived from the instant invention are simply research intermediates that may help scientists isolate the gene and conduct further experimentation. Such probes can only be used to detect or amplify the genetic material having the same structure as the probes themselves. The probes, vectors and gene expression inhibition systems would provide no immediate, real-world information about the overall structure or function of the underlying gene, for example, aside from its expression patterns.

Neither the instant specification nor the prior art presents any evidence that instant SEQ ID NO:142700, much less the claimed RNA equivalents thereof have any specific biological function. No evidence or information is found either in the specification or the prior art linking SEQ ID NO:142700 or its RNA with the modulation of any bacterial or mammalian gene or with the conditions that render cells or hosts susceptible to any disease or disorder, for example. No convincing evidence is found teaching any biological function for SEQ ID NO:142700 at all. In fact, no evidence is found suggesting or stating that the RNAs encoded by SEQ ID NO:142700 have been made, isolated, cloned, detected, expressed, or even analyzed in any living cell *in vitro* or *in vivo*.

In summary, no biological or biochemical function has been assigned to the claimed sequences, apart from the general assertions that it, like the thousands of other sequences described in the sequence listing, may correspond to an miRNA and have some direct or indirect relation to human biology and/or cell function.

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Thus, the proposed utility of the sequences as therapeutic targets or agents, research tools, material resources for preparing diagnostic probes, vectors, and systems, are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acid sequences.

Brenner v. Manson, 148 U.S.P.Q. 689 (U.S. 1966)

The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point—where specific benefit exists in currently available form—there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.

...a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.

Thus, the specification does not teach a specific, substantial, or credible utility for claimed sequences. No target gene has been conclusively identified nor has any evidence been presented linking SEQ ID NO:142700 (or RNA equivalent) or the RNA encoded by SEQ ID NO:142700 with any target gene, nor any evidence showing or suggesting that any small RNAs are expressed by SEQ ID NO:142700 in any cell, and, if so, what function these sequences perform. A credible, specific, and substantial nexus has not been established.

Claims 69-86 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or, alternatively, a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

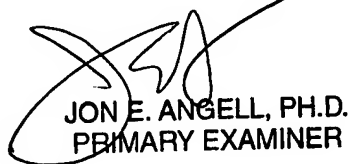
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on 9:00 a.m.- 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JEA


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